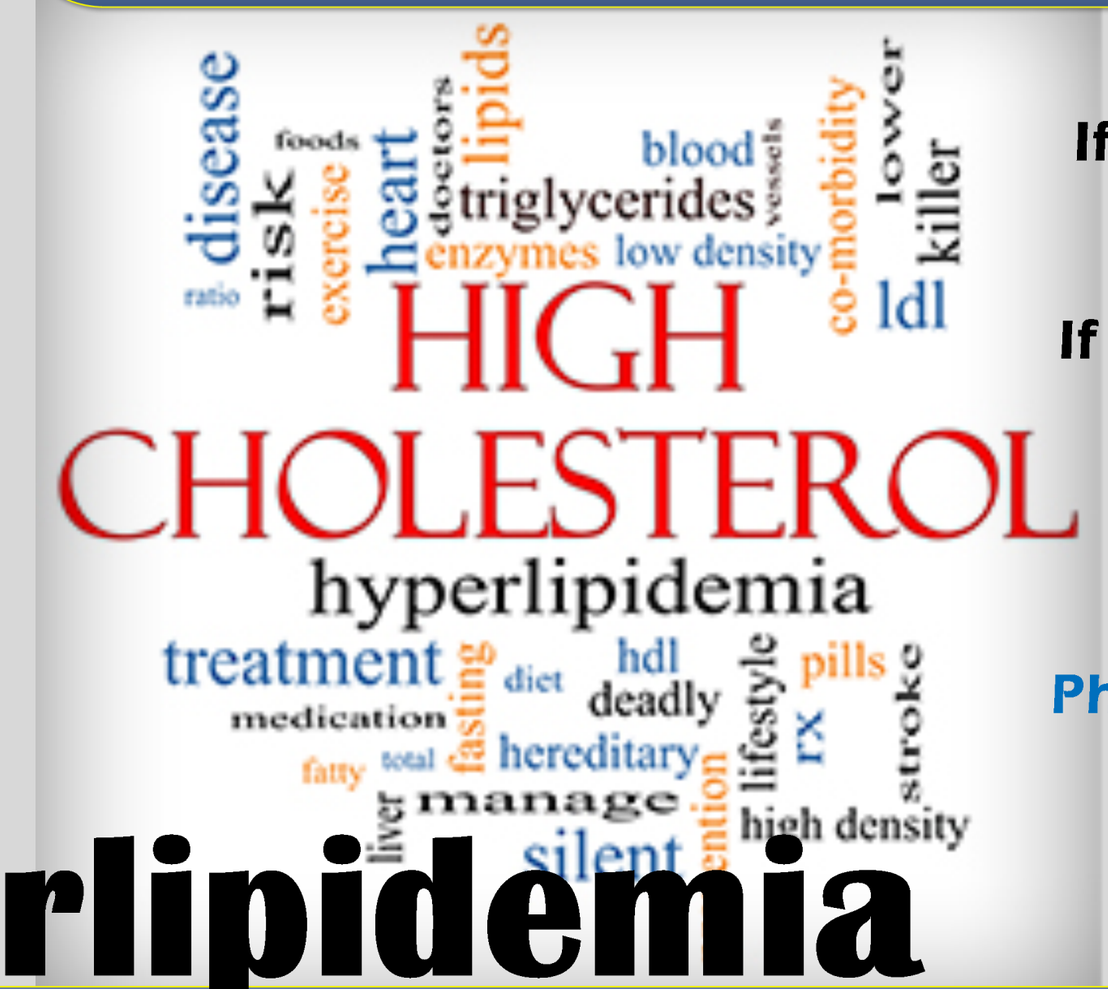
Draw **Pharmacology** *in your mind*



Hyperlipidemia

If you are a pharmacy student
If you are postgraduate and want to revise pharmacology by an easy way
If you are using any pharmacology reference
this file will aid you
> And wait for more <

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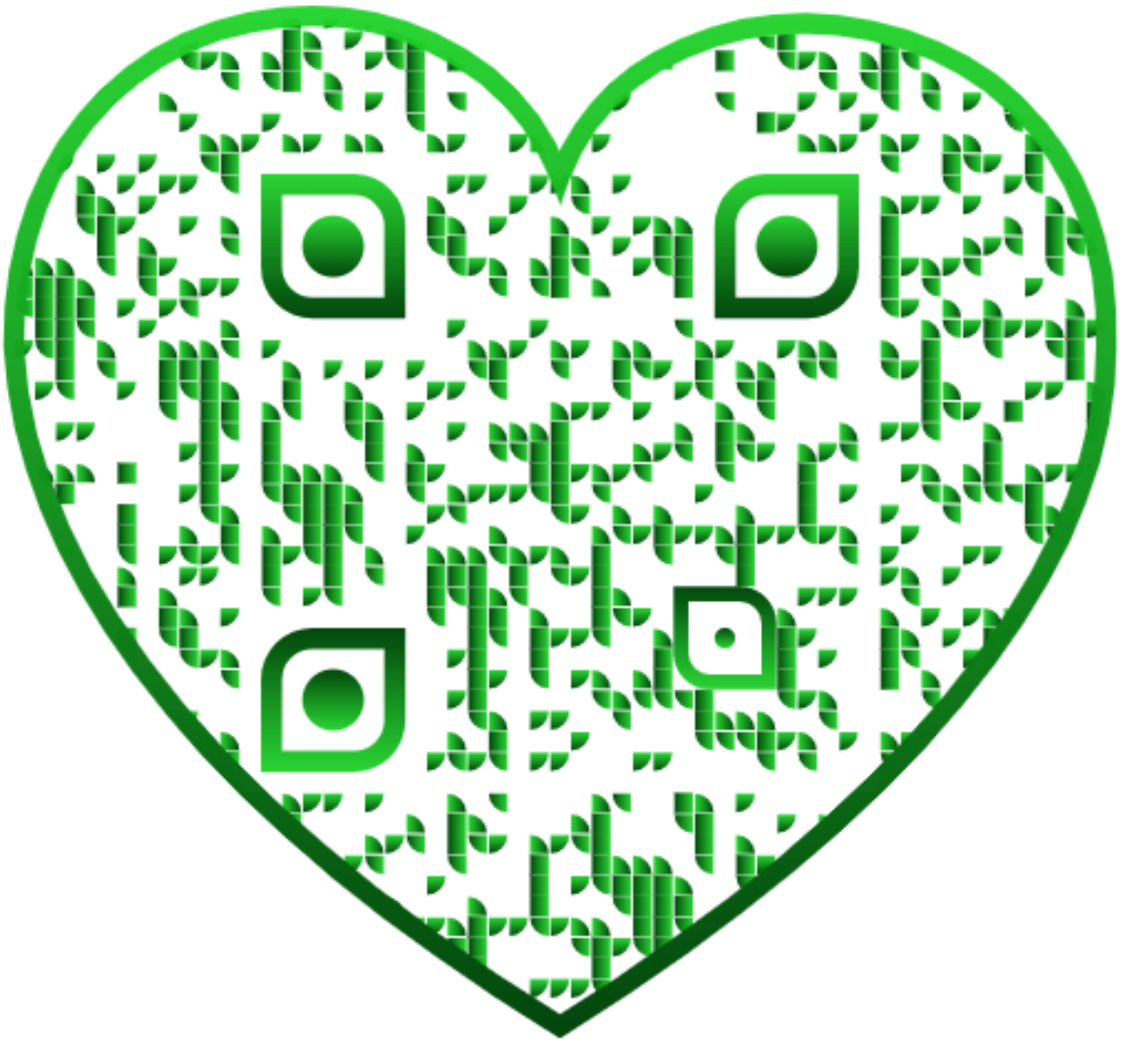
لا تنسونى من صالح دعائكم

Pharmacist. **Alaa Nasr**

د. آلاء نصر



- **Hyperlipidemia** is simply the presence of excess (hyper) amounts of lipids in plasma → it usually causes **atherosclerosis**
- Hyperlipidemia is connected to **coronary heart disease (CHD)**

Coronary heart disease (CHD)

is the cause of about half of all deaths in the United States.

- The incidence of CHD is correlated with **elevated** levels of low-density lipoprotein **(LDL)** cholesterol and **triacylglycerols** and with **low levels** of high-density lipoprotein **(HDL)** cholesterol.
- **Other risk factors for CHD** include cigarette smoking, hypertension, obesity, and diabetes.
- Cholesterol levels may be elevated as a result of an individual's **lifestyle** *(for example, by lack of exercise and consumption of a diet containing excess saturated fatty acids)*.
- Hyperlipidemias can also result from a single inherited **gene defect** in lipoprotein metabolism or, more commonly, from a combination of genetic and lifestyle factors.
- Appropriate lifestyle changes in combination with drug therapy can lead to a decline in the progression of coronary plaque, regression of preexisting lesions, and reduction in mortality due to CHD by 30 to 40 percent.

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Plasma lipids

Consist mostly of **lipoproteins spherical macromolecular** → complexes of lipids and specific proteins (apolipoproteins).

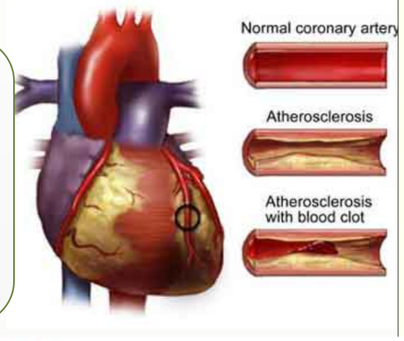
- The clinically important lipoproteins, listed in decreasing order of atherogenicity, are → LDL, very-low-density lipoprotein (VLDL) and chylomicrons, and HDL
- The occurrence of CHD is positively associated with high total cholesterol, and even more strongly with elevated LDL cholesterol in the blood.
- In contrast to LDL cholesterol, high levels of HDL cholesterol have been associated with a decreased risk for heart disease
- *Recommendations for the reduction of LDL cholesterol to specific target levels are influenced by the coexistence of CHD and the number of other cardiac risk factors.*
- *The higher the overall risk of heart disease, the more aggressive the recommended LDL-lowering therapy.*

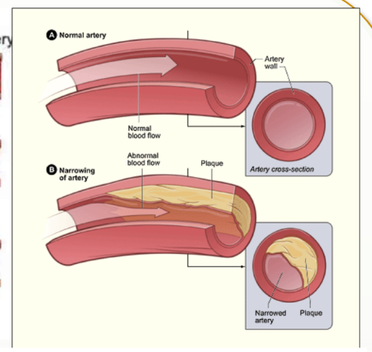
- **LDL** → transfers cholesterols from the liver to peripheral tissues → Bad cholesterol
- **HDL** → transfers cholesterol from peripheral tissues to the liver → Good cholesterol

Atherosclerosis

is a disorder in which lipid deposits accumulate on the lining of the blood vessels, eventually producing degenerative changes and **obstruction** of blood flow.

- Atherosclerosis is considered to be a major contributor in the development of heart disese.
- Hyperlipidemia, particularly elevated serum **cholesterol** and **LDL** levels, is a risk factor in the development of atherosclerotic heart disease





Hyperlipoproteinemias

Phenotype	Generic Designation	Elevated Lipoprotein Class	Elevated Lipid Class	Primary Genetic Disorders
I	Exogenous hyperlipemia	Chylomicrons	Triglycerides	Familial lipoprotein lipase deficiency Familial apolipoprotein C-II deficiency Unclassified
II-a	Hypercholesterolemia	LDL	Cholesterol	Familial hypercholesterolemia Familial combined hyperlipidemia Polygenic hypercholesterolemia
II-b	Combined hyperlipidemia	LDL, VLDL	Cholesterol, Triglycerides	Familial combined hyperlipidemia Unclassified
III	Remnant hyperlipidemia	β-VLDL	Triglycerides, Cholesterol	Familial dysbetalipoproteinemia Unclassified
IV	Endogenous hyperlipemia	VLDL	Triglycerides	Familial hypertriglyceridemia (mild) Familial combined hyperlipidemia Sporadic hypertriglyceridemia Tangier disease
V	Mixed hyperlipemia	VLDL, Chylomicrons	Triglycerides, Cholesterol	Familial hypertriglyceridemia (severe) Familial lipoprotein lipase deficiency Familial apolipoprotein C-II deficiency

Cholesterol level analysis

LDL
- < 100 → Optimal
- 100 - 129 → Near optimal
- 130 - 159 → Borderline
- 160 - 189 → High
- ≥ 190 → Very high

HDL
- < 40 → Low
- ≥ 60 → High

Total Cholesterol
- < 200 → Optimal
- 200 - 239 → Borderline
- ≥ 240 → High

Serum triglycerides
- < 150 → Normal
- 150 - 199 → Borderline
- 200 - 499 → High
- ≥ 500 → Very high

Dietary sources of Cholesterol

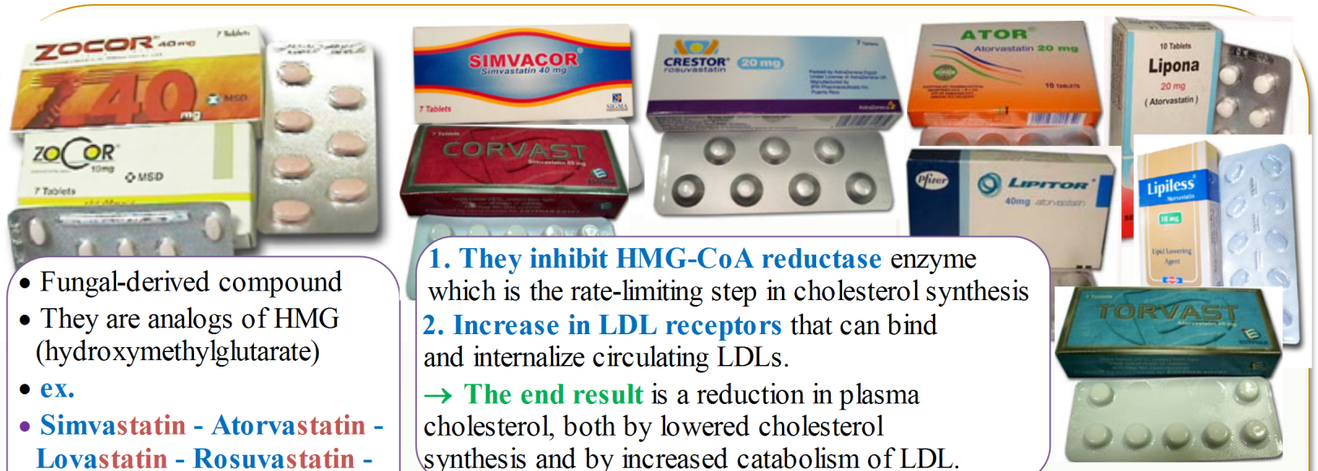
Type of Fat	Main Source	Effect on Cholesterol levels
Monounsaturated	Olives, olive oil, canola oil, peanut oil, cashews, almonds, peanuts and most other nuts; avocados	Lowers LDL, Raises HDL
Polyunsaturated	Corn, soybean, safflower and cottonseed oil; fish	Lowers LDL, Raises HDL
Saturated	Whole milk, butter, cheese, and ice cream; red meat; chocolate; coconuts, coconut milk, coconut oil , egg yolks, chicken skin	Raises both LDL and HDL
Trans	Most margarines; vegetable shortening; partially hydrogenated vegetable oil; deep-fried chips; many fast foods; most commercial baked goods	Raises LDL

Risk factors

Family history of early heart disease *(father before the age of 55 yrs and mother before the age of 55 yrs)* / Cigarette smoking / High blood pressure / Age (men older than 45 years and women older than 55 years) / Low HDL levels / Obesity / Diabetes / Sedentary life style / Excessive consumption of saturated fatty acids

Anti-hyperlipidemics

1. HMG-CoA reductase inhibitors (Statins)



- Fungal-derived compound
- They are analogs of HMG (hydroxymethylglutarate)
- **ex.**
- **Simvastatin - Atorvastatin - Lovastatin - Rosuvastatin - Pravastatin**

1. They inhibit HMG-CoA reductase enzyme which is the rate-limiting step in cholesterol synthesis
2. Increase in LDL receptors that can bind and internalize circulating LDLs.
→ **The end result** is a reduction in plasma cholesterol, both by lowered cholesterol synthesis and by increased catabolism of LDL.

Mechanism

Uses

Effective for all types of hyperlipidemia

Pharmacokinetics

- Extensive first pass effect
- Excreted mainly through bile and small part through urine

Adverse effects

- **Impairing liver function** → this is resolved upon **stopping** the drug use
→ So, serum **transaminase** level should be periodically determined
- **Skeletal muscle myopathy and rhabdomyolysis** *(disintegration or dissolution of muscle) have been reported only rarely.)*
→ This effect is more pronounced in case of renal insufficiency
→→ may appear as a **reddish-brown urine** !! (important)
Myoglobin نتيجة تحلل العضلة و خروج ال
منها و نزولها مع البول
→ So, serum **creatin kinase** should be periodically determined

Contraindications

- Contraindicated in pregnancy, nursing mothers, children & teenagers

- **Note..**
- **Lovastatin and simvastatin** are lactones that are **hydrolyzed to the active** drug. **Pravastatin and fluvastatin** are **active** as such.

- Rosuvastatin and atorvastatin are the most potent LDL cholesterol lowering statin drugs, **followed by** simvastatin, pravastatin **and then** lovastatin and fluvastatin.

Patient education

- Lovastatin is taken once daily, preferably with the evening meal. Fluvastatin, pravastatin, and simvastatin are taken, without regard to meals, once daily in the evening or at bedtime.
- With a bile acid sequestrant, take fluvastatin 2 hours after the bile acid sequestrant and pravastatin at least 4 hours afterward.
- Contact the primary health care provider if nausea; vomiting; muscle pain, tenderness, or weakness occurs.

2. Fibrates

Work in a variety of ways.
- **Clofibrate** → acts to stimulate the liver to increase breakdown of very-low-density lipoproteins (VLDL) to low-density lipoproteins (LDL), decreasing liver synthesis of VLDL and inhibiting cholesterol formation.
- **Fenofibrate** → acts by reducing VLDL and stimulating the catabolism of triglyceride-rich lipoproteins, resulting in a decrease in plasma triglyceride and cholesterol.
- **Gemfibrozil** (Lopid) → increases the excretion of cholesterol in the feces and reduces the production of triglycerides by the liver, thus lowering serum lipid levels.

Mechanism

- **Clofibrate - Fenofibrate - Gemfibrozil**

Uses

For hyperlipidemias associated with increased level of TG (type I , III , VI , V)

Adverse effects

- Clofibrate, fenofibrate, and gemfibrozil may increase cholesterol excretion into the bile, leading to → **cholelithiasis** or cholecystitis → If cholelithiasis is found, use of the drug is discontinued.
- **Myositis** and in some cases myopathy and rhabdomyolysis *(risk is increased upon co-administration of HMG-CoA inhibitors)*

Contraindications

- Pregnancy
- Pre-exsiting gall bladder disease

Drug-interactions

- They compete with Coumarines *(Warfarin → so increase the risk of bleeding)* and Sulphonylurea for plasma protein binding sites

Patient education

- Clofibrate → If gastrointestinal upset occurs, take the drug with food. Notify the primary health care provider if chest pain, shortness of breath, palpitations, nausea, vomiting, fever, chills, or sore throat occurs.

- Gemfibrozil → Dizziness or blurred vision may occur. Observe caution when driving or performing hazardous tasks. Notify the primary health care provider if epigastric pain, diarrhea, nausea, or vomiting occurs.

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Anti-hyperlipidemics

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TYPE OF DRUG	EFFECT ON LDL	EFFECT ON HDL	EFFECT ON TRIACYLGLYCEROLS
HMG CoA reducatase inhibitors (statins)	↓↓↓↓	↑↑	↓↓
Fibrates	↓	↑↑↑	↓↓↓↓
Niacin	↓↓	↑↑↑↑	↓↓↓
Bile acid sequestrants	↓↓↓	↑	Minimal
Cholesterol absorption inhibitor	↓	↑	↓

3. Niacin (Nicotinic acid) Vitamine B_3

Mechanism

1. Niacin strongly **inhibits lipolysis in adipose tissue** → the primary producer of circulating free fatty acids → which the liver normally utilizes as a major precursor for triacylglycerol synthesis which is required for VLDL production. → **So, ⇓ TGs → ⇓ VLDL → ⇓ LDL**

2. Increase **HDL**

3. Nicotinic acid can **⇓ the thrombotic consequences** of hypercolesteremia by:

a) ⇑ level of tissue plasminogen activator

b) ⇓ fibrinogen level

Uses

For hyperlipidemias associated with increased level of TG (type I , III , VI , V)

Adverse effects

1. Cutaneous flush and pruritis → this is mediated through prostaglandins → so, can be relieved by prior administration of Aspirin

2. Impaired tubular secretion of uric acid → so, can predispose gout

3. Impaired glucose tolerance

4. Hepatotoxicity

Patient education

- Nicotinic acid →Take this drug with meals. This drug may cause mild to severe facial flushing, feeling of warmth, severe itching, or headache. These symptoms usually subside with continued therapy.

- The primary health care provider may prescribe aspirin (325 mg) to be taken about 30 minutes before nicotinic acid to decrease the flushing reaction. If dizziness occurs, avoid sudden changes in posture.

5. Colesterol absorption inhibitors

Ezetimide

Mechanism

Selectively inhibits intestinal absorption of dietary and biliary cholesterol in the small intestine, → leading to a decrease in the delivery of intestinal cholesterol to the liver → this causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood

Contraindications

Patients with liver impaired function

• **Note..**

- Ezetimibe has no clinically meaningful effect on the plasma concentrations of the fat-soluble vitamins.

- A formulation of **ezetimibe and simvastatin or atorvastatin** has been shown to lower LDL levels more effectively than the statin alone.

4. Bile acid sequestering agents

Mechanism

- These drugs **bind to bile acids** to → forming an **insoluble substance** that cannot be absorbed by the intestine, → so it is secreted in the feces.

- With increased loss of bile acids, → the liver uses cholesterol to manufacture more bile →This is followed by a decrease in cholesterol levels.

Examples

Cholestyramine - Colestipol

Uses

- The bile acid sequestrants are used as **adjunctive therapy** for the reduction of elevated serum cholesterol in patients with hypercholesterolemia who do not have an adequate response to a diet and exercise program .

- Cholestyramine may also be used to relieve pruritis associated with partial biliary obstruction.

Adverse effects

1. A common problem associated with the administration of the bile acid sequestrants is **constipation** → constipation may be severe and may occasionally result in fecal impaction. Hemorrhoids may be aggravated.

2. Impaired absorption of fat-soluble vitamins **(K - E - D - A)**

3. Impaired absorption of some **concurrently administered drugs** such as → Pravastatin, Warfarin, digoxin, thiazide diuretics, penicillin, propranolol,tetracyclines, folic acid, and the thyroid hormones, → resulting in decreased effects of these drugs.

→ **Solution** → drugs should be given **1-2 hours before** or **4-6 hours after** the administration of bile acid sequestering resins

Pharmacokinetics

- Anion exchange resins
- Not absorbed orally

Patient education

- Take the drug before meals unless the primary health care provider directs other ways.

- Cholestyramine powder →The prescribed dose must be mixed in 4 to 6 fluid ounces of water or non-carbonated beverage and shaken vigorously.

- The powder can also be mixed with highly fluid soups , The powder should not be ingested in the dry form

- Other drugs are taken 1 hour before or 4 to 6 hours after cholestyramine.